Vaccine controversies: a clinician's dilemma

Vaccination had enjoyed a distinguished history long before the discovery of antimicrobial agents. In 1798, Edward Jenner demonstrated that cowpox virus protected against smallpox—a scourge of mankind. A more recent landmark occurred in 1954 with Jonas Salk's vaccine which proved highly effective against the polio virus. Midway between these two events, in 1885, Louis Pasteur began a vaccine series to prevent rabies in a young boy suffering from multiple serious bite wounds by a mad dog. This proved lifesaving. The following is a quote from a publication on the subject:

> Pasteur, faced with a small boy who was in great pain from multiple serious bite wounds, was faced also with the most agonizing decision of his career. He had at his disposal a post-exposure vaccine which he knew to be efficacious with dogs. It had never been tested in humans.
>
> After two weeks of injections of increasing strengths, Pasteur's anguish increasing with the increasing virulence of the inoculum, the child's wounds were healing. He continued in perfect health. The night before the last fully virulent injection, Pasteur was unable to sleep tormented by visions of what might conceivably happen to Joseph Meister. Nothing happened. Both Joseph survived and so did Jean-Baptiste Jupille, the brave shepherd boy from the Jura, who was treated by Pasteur three months later. These two initial successes established Pasteur in the eyes of the world as a savior of those bitten by mad dogs.[1]

A vaccine must prove itself through "yes" answers to the following important questions:

- Is it immunogenic?
- It is protective?
- Is it safe?
- Is it inexpensive to manufacture?
- More basic in consideration: Is the risk of the disease worth the benefit of the vaccine?

Pasteur's vaccine appeared to be immunogenic, protective, and reasonably inexpensive. Although some questions remained about its safety, the vaccine was largely accepted by the profession. Rabies was a recognized killer for which there was no treatment.

Targeting a vaccine that will truly be beneficial for a population is essential. For example, if one had an effective vaccine against cytomegalovirus (CMV), who would be the candidates? CMV is currently a most significant infectious disease problem in highly immunocompromised patients, such as organ transplant recipients and victims of acquired immunodeficiency syndrome (AIDS). In addition, CMV acquired neonatally may cause long-term effects, such as mental retardation and deafness, in offspring. One would first note that natural CMV is extremely ubiquitous, varying in prevalence according to age, geography, and socioeconomic class of a population. By and large, CMV infection is common and usually benign. Such a vaccine would need to be targeted for a susceptible population predictably likely to have significant disease from the infection, but at the same time, capable of making a normal immune response. What a challenge for investigators!

Vaccines are classified according to whether they are "active" (composed of live attenuated micro-organisms) or "inactive" (products of intact or pieces of killed micro-organisms). They are also designated as "general purpose" (desirable for an entire population) or "special purpose" (desirable for a select population). No adult needs to suffer from tetanus, measles, mumps, rubella, or polio. Excellent general purpose vaccines are available to prevent these infections. However, when one considers some of the special-purpose vaccines now available for adults, indications seem ill-defined and the effects seem controversial. Let us examine influenza, pneumococcal, and hepatitis B vaccines.

Influenza vaccine

Influenza vaccines are composed of recently prevalent influenza A and B viruses inactivated in formaldehyde solution. A major drawback to this vaccine is the extreme antigenic lability of the influenza A virus. As antigenic drifts occur within influenza A hemagglutinins and neuraminidases, the vaccines become rapidly outdated.[2] Although 85% of vaccinates develop antibodies after vaccination, only 70% are protected after exposure to natural infection. Annual influenza vaccination is required because of ever-changing antigen structures. Although national concern was raised about the safety of the swine influenza vaccine given in the late 1970s, influenza vaccines in recent years appear to be as safe as any currently on the market. Indications for annual influenza vaccination have included patients with cardiopulmonary disease, chronic renal disease, diabetes mellitus, chronic anemia, and immune deficiency. Many of these patients are not capable of mounting an appropriate immune response to vaccination; perhaps less than 50% of those vaccinated will be protected after exposure to influenza. Does this mean that we should continue to vaccinate all these individuals every year? To my knowledge, it has not been shown that the influenza vaccine substantially reduces mortality from influenza in immunocompromised patients. Nevertheless, most vaccine candidates are not immunosuppressed, and within this group, we must now consider ourselves, as health care providers, prime candidates. This somewhat bold recommendation has recently come from the Immunization Practices Advisory Committee.[3] Why risk the chance of spreading disease to our patients on hospital rounds or in the office?

Pneumococcal vaccine

Because of a continued unacceptably high mortality from pneumococcal infection, a resurgence of interest in a pneumococcal vaccine occurred in the early 1970s. A polyvalent vaccine was licensed for use in the United States in 1977.[4] The vaccine now contains 23 serotypes of pneumococcal capsular polysaccharides. Vaccination by single injection is recommended for patients who appear at greater risk of serious pneumococcal disease than the general population. Such patients who have underlying lung disease (chronic obstructive pulmonary disease) or immunologic problems (i.e., postsplenectomy) are considered prime candidates for the vaccine. Although a booster injection may be desirable because of waning antibody levels, it is not recommended because significant side effects have occurred after reinoculation.[5] Serum antibody levels following immunization in healthy volunteers have previously been considered protective. However, more recently, critics point out that antibody levels by themselves do not correlate with protection from disease.[6] Furthermore, many diseases or conditions for which the vaccine is indicated are associated with an underlying immunodeficiency. For example, patients with Hodgkin's disease treated with chemotherapy and radiation have lower antibody titers after vaccination. Similar findings are noted in postsplenectomized patients; those on chronic hemodialysis; and those with sickle cell disease, multiple myeloma, and systemic lupus erythematosis. Perhaps a pneumococcal vaccine should not have been approved in these groups of patients until it was proved effective by carefully conducted studies.[7] Hirschmann and Lipsky[6] provided a critical review of the pneumococcal vaccine in the United States and concluded that "an analysis of all of the information currently available indicates that in the United States and perhaps other highly industrialized nations, scientific evidence supports pneumococcal vaccination only for patients with sickle cell anemia." Presently, the vaccine is prescribed by many of us, at best, with cautious optimism. A recent study suggests that vaccine efficacy was 0% in severely immunocompromised patients; on the other hand, it was 77% for otherwise healthy patients at moderately increased risk of pneumococcal infection.[8] Certainly, the vaccine is clearly indicated in adults with cardiovascular or pulmonary disease when pneumococcal infection remains a significant cause of morbidity and mortality.[5]

Hepatitis B vaccine

The licensure of hepatitis B virus (HBV) vaccine in 1981 was a significant event for all in the health care field. Those of us who have sustained exposure to blood and blood products during our daily professional life are prime candidates for the vaccine. The vaccine is manufactured from hepatitis B surface antigen that is obtained by plasmapheresis from otherwise healthy carriers of hepatitis B virus. Noninfectious particles are extracted, purified, and inactivated by a tedious, extensive, and expensive process. In field

trials, 95% of recipients demonstrated antibody response following a three-injection series.[9] The protective effect of this vaccine was striking after natural HBV exposure. Here is a vaccine that is purified and inactivated to the highest degree technologically possible and is immunogenic and protective. Yet, the HBV vaccine has not been widely accepted by the medical community.[10] Concerns have been raised about the possible transmission of AIDS to those being vaccinated. In the early field trials, both vaccinates and control patients were at high risk for the development of AIDS; however, AIDS occurred with no greater frequency in the former group.[11] In later studies of health care workers who were not at high risk for the development of AIDS, no cases of AIDS were reported.[12] Nevertheless, feelings remain strong about the theoretical potential for transmission of AIDS or other infectious agents that are simply not detectable with present technology. Furthermore, the manufacturing process for the HBV vaccine is expensive; a three-injection series costs approximately $100. These concerns have stimulated development of alternative HBV vaccines, using innovative technologies.[13] One method takes the "S gene" from HBV, which directs synthesis of hepatitis B surface antigen, and introduces it into bacteria, yeasts, or mammalian cells, thus directing them to manufacture the antigen. This technique results in higher concentrations of antigen than by the current method. Perhaps the most exciting new vaccine being developed is one that is totally synthetic. Polypeptides conceived by protein engineering can be made immunogenic against HBV. If shown to be protective, polypeptide vaccines are likely to be the safest and easiest to manufacture.

I am often asked if I have taken the current HBV vaccine. My response has been to simply ask the questioner if he or she is exposed to blood or blood products on a regular basis. If so, I tell him or her to get vaccinated. I have not taken the vaccine because I am not regularly exposed to blood and blood products. Since I am not a vaccine candidate, am I more objective about recommending who should have and who shouldn't have the vaccine? How curious it is that vaccines continue to be associated with controversy, dogma, and doubt. Nevertheless, our scientific accomplishments in this field, particularly with the exciting prospects of synthetic vaccines, would be of great envy to Jenner and Pasteur.

THOMAS F. KEYS, M.D.
Department of Infectious Disease
The Cleveland Clinic Foundation
9500 Euclid Ave.
Cleveland OH 44106

References

1. Waterson AP, Wilkinson L. An introduction to the history of virology. Cambridge, England, Cambridge University Press, 1978, p 58.
2. Nolan TF Jr. Influenza vaccine efficacy. JAMA 1981; **245:**1762.
3. Immunization Practices Advisory Committee (ACIP). Prevention and control of influenza. MMWR 1984; **33:**253–266.
4. Austrian R. Pneumococcal vaccine: development and prospects. Am J Med 1979; **67:**547–549.
5. Immunization Practices Advisory Committee (ACIP). Update: pneumococcal polysaccharide vaccine usage—United States. MMWR 1984; **33:**273–281.
6. Hirschmann JV, Lipsky BA. Pneumococcal vaccine in the United States: a critical analysis. JAMA 1981; **246:**1428–1432.
7. Broome CV. Efficacy of pneumococcal polysaccharide vaccines. Rev Infect Dis 1981; **3:**S82–S88.
8. Shapiro ED, Clemens JD. A controlled evaluation of the protective efficacy of pneumococcal vaccine for patients at high risk for serious pneumococcal infections. Ann Intern Med (in press)
9. Szmuness W, Stevens CE, Zang EA, Harley EJ, Kellner A. A controlled clinical trial of the efficacy of the hepatitis B vaccine (Heptavax B): a final report. Hepatology 1981; **1:**377–385.
10. Palmer DL, King R. Attitude toward hepatitis vaccination among high-risk hospital employees (letter). J Infect Dis 1983; **147:**1120–1121.
11. Immunization Practices Advisory Committee (ACIP). The safety of hepatitis B virus vaccine. MMWR 1983; **32:**134–136.
12. Oxman MN. Hepatitis B vaccination of high-risk hospital personnel (editorial). Anesthesiology 1984; **60:**1–3.
13. Kit M, Kit S. Viral vaccines. Med Clin North Am 1983; **67:**1129–1145.